EXHIBIT B

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2005 IUGA GRAFTS ROUNDTABLE

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Clinical implications of the biology of grafts: conclusions of the 2005 IUGA Grafts Roundtable

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Abstract With few exceptions, the current expansion of graft utilization in pelvic reconstructive surgery is not a product of evidence-based medicine. Abdominal sacrocolpopexy and suburethral sling procedures are two situations under which synthetic graft utilization is indicated, based on randomized prospective trials and reported clinical outcomes. Otherwise, indications and contraindications for graft utilization are unclear. Current published data on the biology of synthetic and biologic grafts are limited and overall not very helpful to the reconstructive surgeon who is faced with the selection of a graft for use during a reconstructive procedure. This Roundtable presented the opportunity for a series of basic science researchers to present their data to a group of reconstructive surgeons and provide publishable background information on the various currently available grafts. The occurrence of healing abnormalities after graft implantation is becoming increasingly recognized as a potentially serious problem. To date, definitions and a classification system for healing abnormalities do not exist. Based on the input from basic scientists and experienced surgeons, a simple classification is suggested based on the site of healing abnormality, timing relative to graft implantation, presence of inflammatory changes, and the viscera into which the graft is exposed. Many opportunities for clinical and basic science research exist. As the use of grafts in reconstructive surgery is expanded, surgeons are encouraged to familiarize themselves with currently published data, and determine whether a graft should, or should not be, utilized during a reconstructive procedure, and if so, the type of graft best indicated in each specific clinical situation.

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Conclusions of the Roundtable

The Grafts Roundtable provided a unique opportunity for an exchange of knowledge and ideas between basic science researchers and pelvic reconstructive surgeons. Although industry and current clinical trends suggest that graft materials could be used in all cases of reconstructive pelvic surgery, the Roundtable attendees acknowledged that presently there is no evidence-based medicine to justify a move in this direction. For the use of a graft to be considered, various factors should be present, including: the presenting compartment being at least to the introitus or beyond, the prolapse having a significant negative impact on the patient's quality of life, and inadequacy in the quality of the patient's endogenous tissues for a non-grafted repair. Abdominal sacrocolpopexy and suburethral sling procedures represent clinical situations where prospective randomized trials as well as published prospective series have demonstrated the need for a graft and the superiority of a synthetic graft over a biologic graft. Apart from these two situations, the reported indications for graft utilization are not clear and not universally recognized.

It was the consensus of this group that not all patients undergoing a reconstructive procedure for genital prolapse require the use of a graft. As more literature is published, it is likely that clearer graft utilization indications will eventually develop. In all likelihood, indications for graft utilization will be better delineated and limited to specific clinical situations. The risk/benefit ratio of graft utilization, as with any clinical intervention, will be clarified as short- and long-term benefits of graft use is balanced with short-

and long-term risks of graft implantation. Moreover, the technique for graft implantation might have as important a role in long-term success as the actual makeup of the graft itself. This adds a significant variable, which requires further study. New techniques, such as transobturator and infracoccygeal routes for graft placement, have not yet been demonstrated to improve the outcomes of reconstructive pelvic surgery, whether grafted or not.

Currently accepted relative contraindications to the use of biomaterials have been suggested (Table 1). However, it was also appreciated that some of the above conditions represent a patient at a high risk for failure of a traditional prolapse repair, and that these situations might present a case where the use of a graft would be recommended by some surgeons. Resolution of some of these contraindications may occur with medical therapy (i.e., treatment of severe atrophy with local estrogen or vaginal infection with antibiotics). Others, however, are not reversible and may actually be progressive leading to an increasingly high risk of healing abnormalities (i.e., pelvic radiation with progressive devascularization). In many of these high-risk situations, graft utilization should be individualized, and preference may be given to the use of a biologic graft.

During this Roundtable, a series of observations were made based on the previous presentations by basic science researchers and the surgeons' clinical experiences. These include:

1. Integration of a graft into host tissue is important. The implanted graft should allow for prompt collagen in-growth and neovascularization. This should occur without the occurrence of infection or significant inflammatory reaction. A limited amount of inflammatory reaction is necessary to promote neovascularization and collagen in-growth. Grafts that are poorly integrated include microporous synthetic grafts and biologic grafts treated with chemical cross-linking. These grafts may become encapsulated, leading to hardening, shrinkage, and other graft changes, which may subsequently lead to dyspareunia, alteration of normal anatomy, and increased risk of failure. Attempts at improving integration of cross-linked biologic grafts, such as by placing holes within the graft, appear to improve their utility. However, long-term data are lacking. Microporous synthetic grafts are more likely to become infected and, thus, should not be utilized in the pelvis. Currently available monofilament, macroporous synthetic grafts, and non-cross-linked biologic grafts appear to be well-integrated into host tissues. A potential drawback to biologic non-cross-linked grafts relates to rapid metabolism and enzymatic degradation of the graft, which may occur before appropriate integration in a small percentage of patients.
2. Currently existing graft classification systems do not apply to the use of grafts in the pelvis. The Amid classification published in 1997 is frequently quoted as the accepted classification system for synthetic grafts (see Dwyer and Deprest contributions). As only Type 1 mesh is recommended for use in the pelvis, this classification does not, in general, apply to the use of synthetic grafts in the pelvis. There are currently multiple subtypes of Type 1 mesh, with markedly variable physical characteristics, including softness, weave, elasticity, and pore size, among others. There are, thus, great and clinically significant differences among Type 1 synthetic mesh materials. To improve clarity when referring to Type 1 mesh, other physical characteristics of the mesh should be described. Clear examples of these characteristics include directionality and distortion with the stretch, which can play a significant role in the outcomes of a suburethral sling procedure.
3. Evaluation of biologic grafts poses a more complex clinical challenge. Unlike synthetic grafts where composition and physical characteristics are the only significant variables, biologic grafts have a number of other characteristics, which should be considered when selecting a graft for surgical implantation.

    a. The biologic source may have a significant impact on how the graft behaves after implantation. Unpredictable graft quality has led to a decline in the use of human tissue banked grafts in preference of xenografts of more predictable integrity. Whether a porcine, bovine, or other animal source is preferable for use in the pelvis is unclear. Whether a dermal, pericardial, dural, or other anatomic source is preferable is also unclear. A great amount of work is needed in clarifying the preferred source of a biologic graft.
    b. Graft preparation is highly variable. Chemical denaturation of a graft eliminates cellular components which may predispose to immune reactivity. However, it may also weaken the integrity of a graft and alter its integration into host tissues. Irradiation of biologic grafts has been demonstrated to weaken a graft and reduce its integrity. Less is known about the impact of chemical treatment of a graft in preparation for implantation. The current concept that a non-cross-linked graft is preferable for use in the pelvis is based primarily on a theoretical basis. Comparative trials will be necessary to determine the optimal pre-implantation treatment of a biologic graft.

Table 1 Relative contraindications to the use of biomaterials

1. History of previous pelvic radiation
2. Severe urogenital atrophy
3. Immunosuppressed patient
4. Presence of active pelvic or vaginal infection
5. Patient currently on systemic steroids
6. Host factors including:
a. Poorly controlled diabetes
b. Morbid obesity
c. Heavy smokers

c. The rate of graft degradation after implantation is poorly understood. A graft that undergoes enzymatic degradation too rapidly, may not allow for collagen in-growth and may not be successful in enhancing the efficacy of the repair. Host and graft factors, which impact graft degradation and integration, are very poorly understood and require more study. In particular, the role of specific host enzymes implicated in graft breakdown requires further analysis and understanding. Some of these factors may be identifiable pre-implantation, and even modifiable.

4. Rat biology does not always equal human biology. Animal models have been developed for evaluation of hernia repair techniques and the use of grafts in hernia surgery. These models may be helpful in evaluating tensile strength and graft incorporation. However, their utility in assessing likelihood of graft infection has no clinical correlation, as certain animal models, such as rats, are not susceptible to tissue infections. Tissue reaction to an implanted graft will also be different in an animal model as compared to a human model. The recognized occurrence of subcutaneous seromas in patients implanted with a biologic collagen matrix has not been reported in animal models and, thus, requires clinical experience in humans to be better understood. Thus, translation of animal biology to human biology is imprecise.
5. Healing abnormalities after graft implantation have various etiologies. Perhaps the most troublesome aspects of the use of grafts in reconstructive surgery relates to the development of healing abnormalities, such as "erosion," "rejection," and "infection." The etiology of these healing abnormalities is poorly understood. We will not be able to minimize their occurrence until we have a better idea of their etiology. Contributing factors likely include bacterial contamination and infection, immune reaction to the graft, and physical interference with the normal healing process. Most healing abnormalities are noted with the use of synthetic polypropylene grafts. These grafts are not apt to get infected, are relatively inert, and do not elicit a significant immune reaction. Other factors must, therefore, be involved in these healing abnormalities. Technical implantation factors, such as separation of a suture line and individual host factors (patients with sensitive skin and/or multiple allergies) are likely significant contributing factors. Much basic work is required in achieving a better understanding of the etiology and management of healing abnormalities.
6. The characteristics of the ideal implant material are unclear. Some were proposed and discussed at this Roundtable (Table 2). It was accepted that currently, the perfect biomaterial does not exist. Also, it was acknowledged that currently available laboratory testing and animal models used in researching biomaterials do not adequately reflect the same environmental challenges that the female pelvis endures during a lifetime.
7. A healing abnormality classification is needed. It was agreed that a standardized classification system would be helpful in describing healing problems and designating a degree of severity. Current terminology is vague and there is lack of consensus as to the definition of the utilized terms. Terms such as "erosion", "rejection," and "exposure" are used frequently. These terms are poorly defined in relation to healing abnormalities associated with the usage of grafts. The participants, therefore, suggested not using these terms and rather adhering to a classification, which would describe a healing abnormality based on four factors:

   a. Time related to implantation
   b. Site of healing abnormality relative to suture line
   c. Presence of inflammatory tissue
   d. Viscera affected

This results in a classification of simple vs complex healing abnormalities, which may also help the surgeon determine a therapeutic plan (Table 3). A simple healing abnormality may require treatment with local estrogen or simple excision of the exposed mesh in the office setting. In some situations, a brief outpatient procedure in the operating room may be required. A complex healing abnormality may require increased diligence, including usage of systemic or local antibiotics, local treatment with chemical or electrocautery, or surgical exploration with the removal of a significant portion or the entire implanted graft. Based on the participants' clinical experience, the vast majority of healing abnormalities are considered simple, based on the above classification. Typically, a Type 1 soft synthetic mesh is not associated with a complex healing abnormality, unless the mesh is visible in the bladder or rectum. The above classification will require clinical scrutiny and validation before widespread acceptance. We consider it a first step in standardizing the

Table 2 "Ideal" biomaterial

Inert
Sterile
Non-carcinogenic
Mechanically durable
Cause no/minimal inflammatory or immune reaction
Inexpensive
Convenient
Easy to use
Readily available
Maintains implanted shape and configuration
(Synthetic) Withstand modification by body tissue
(Biologic) Resist enzymatic breakdown prior to established neovascularization and collagen in-growth

Modified from: Kushner L, Mathrubutham M, Burney T, Greenwald R, Badlani G (2004) Excretion of collagen-derived peptides is increased in women with stress urinary incontinence. Neurourol Urodyn 23(3):198–203

Table 3 Proposed classification of graft-related healing abnormalities

	Simple	Complex
Timing relative to implantation	<12 weeks	>12 weeks
Site relative to suture line	At suture line	Other than at suture line
Presence of inflammatory tissue	None	Granulation
Affected viscera	Vagina	Bladder, rectum or other

reporting of healing abnormalities, which are being seen with increased frequency.

Future needs

Research and clinical trials

A surgeon must consider many, if not all, of the above issues before selecting a graft for implantation during pelvic reconstructive surgery. The basic question of whether a specific patient may benefit from the use of a graft (i.e., indications for graft usage) was not specifically addressed during this Roundtable. Outcomes of future clinical trials will help clarify the specific situations in which a graft may be beneficial. In addition, future trials will also help surgeons achieve a better understanding of the risks associated with graft implantation. Roundtable participants encourage surgeons to initiate randomized clinical trials to evaluate graft usage vs non-usage in specific prolapse repairs. Different types of grafts (synthetic vs biologic) should be analyzed to determine specific applications. This will likely require cooperation between surgeons and clinical centers to achieve enrollment of sufficient patients to reach a statistical significance. Significant challenges are certainly faced by those entertaining performance of a randomized trial. A decision was made to encourage a cooperative effort through IUGA, as well as other professional society memberships, in designing appropriately powered trials to achieve scientifically valid results.

Outcome measures should include anatomic as well as functional parameters over a reasonable observation time period. Quality of life measures should be utilized, and follow-up should extend beyond one year and preferably longer. No specific clinical scenarios were identified as specifically suitable for clinical study. Most surgeons suggested that evaluation of anterior compartment repairs would be most amenable to a multi-center randomized trial.

It is clear that a significant amount of work is necessary in the preclinical testing of materials. This includes biocompatibility studies as well as identification of animal models for fascial repair. It is recognized that more site-specific tests be developed to determine the safety and efficacy of graft materials. This is particularly important in translational research as related to the similarities and differences in the pathophysiology and treatment of abdominal wall hernias as related to genital prolapse. Because many animal studies utilize the abdominal wall hernia model to evaluate a specific graft material, their value in predicting usefulness in vaginal prolapse repair is unclear. In the interim, animal models for vaginal prolapse and correction of such should be searched for and identified. Until those animal models are identified, much of our knowledge will be based primarily on retrospective clinical data. The identification of an animal model is particularly important in increasing our knowledge in healing abnormalities. Experimental models can be created to evaluate the impact of the various factors associated with healing abnormalities noted in the previous section.

It was suggested that centers could be identified for processing and analyzing explanted grafts. As an increasing number of grafts are being explanted because of healing abnormalities, histologic and chemical analysis of the explanted grafts may provide an insight as to the pathophysiology of post-implant problems. Protocols will need to be developed for the processing and description of explanted graft analysis.

Surgeon education

It is clear that surgeons are not sufficiently knowledgeable about the biology of grafts currently being utilized. Surgeon education is critical at this particular junction in the evolution of pelvic reconstructive surgery. The actual nature and biology of currently available grafts should be shared with pelvic reconstructive surgeons. Accurate description of the available types of grafts, as well as their biologic and chemical properties relevant to each application, should be better understood. A surgeon should base his/her selection of biologic or synthetic grafts for a particular use on data, rather than on marketing materials and/or physical feel of the graft. Frequently, a surgeon's choice is based on a simple palpation of the graft and its gross physical properties rather than on the graft's previously described biologic behavior. Surgeons should also consider the long-term consequences of graft implantation. There is much concern regarding the future occurrence of unusual enteroceles and other atypical forms of prolapse due to improper placement or movement of a graft, as well as the possible shrinkage of an implanted graft. Although surgeons are becoming readily skilled at graft implantation, an expertise needs to be developed in the management of complications, including graft explantation when necessary. An important aspect of graft utilization should also be the identification of those situations where grafts should *not* be used. The specific clinical scenarios are currently not well-recognized and are open for discussion.

It is recognized that the absence of knowledge regarding indications for graft usage, specific physical and biologic characteristics of currently available grafts, short- and long-term risks and benefits of graft usage, as well as the optimal

implantation technique poses the most significant barrier to optimal graft utilization. Thus, improving surgeons' knowledge is at the basis of improving outcomes from graft usage, and surgeons should be increasingly inquisitive when considering the use of a graft in reconstructive surgery.

Based on current knowledge, surgeons should not be expected to convert to the uniform use of synthetic and biologic materials for all cases of reconstructive pelvic surgery. It will be through cooperative efforts between surgeons, basic scientists, and industry that our knowledge base will increase to a degree where we will be able to make rational decisions regarding the appropriate usage of grafts in reconstructive pelvic surgery.